IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **Hiroko KOJIMA et al.** Art Unit: **1632**

Application Number: **10/575,474** Examiner: **Wu Cheng Winston Shen**

Filed: **April 12, 2006** Confirmation Number: **3422**

For: **IMPLANT FOR REGENERATING BONE OR CARTILAGE WITH THE USE OF TRANSCRIPTIONAL FACTOR**

Attorney Docket Number: **062405**
Customer Number: **38834**

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Hiroko KOJIMA, a citizen of Japan, hereby declare and state the following:

1. I graduated from the University of Tsukuba of Tsukuba, Ibaraki, Japan in 1998 with a Ph.D. degree in Science.

2. Since 2005, I have been employed by the research and development division of Bio Matrix Research, Inc. of Nagareyama, Chiba, Japan where my present title is Senior Scientist. During my employment therein, I have conducted research and development of diagnosis kits.

3. I am a co-author of the following publications:

H. Kojima, A. Nemoto, T. Uemura, H. Honma, M. Ogura, Y-K Liu, "DRAK1, Death Associated Protein Kinase-Related Apoptosis-Inducing Protein Kinase, is Expressed in Active Osteoclast Strongly and Induces Apoptosis," *J. Biol. Chem*, **276(22)** 19238-19243 (2001).

J. Dong, H. Kojima, T. Uemura, M. Kikuchi, T. Tateishi, J. Tanaka, "In Vivo Evaluation of a Novel Porous Hydroxyapatite to Sustain Osteogenesis of Transplanted Bone Marrow Derived Osteoblastic Cells," *J. Biomed. Matter. Res.* **57**, 208-216 (2001).

Jian Dong, Toshimasa Uemura, Masanori Kikuchi, Junzo Tanaka, Tetsuya Tateishi "Long-term durability of porous hydroxyapatite with low-pressure system to support osteogenesis of mesenchymal stem cells," *Bio-Medical Materials and Engineering,* **Vol. 12, 2** 203 - 209 (2002).

Toshimasa Uemura, Jian Dong, Yichao Wang, Hiroko Kojima, Takashi Saito, Daisuke Iejima, Masanori Kikuchi, Junzo Tanaka, Tetsuya Tateishi, "Transplantation of cultured bone cells using combinations of scaffolds and culture techniques," *Biomaterials*, **24(13)** 2277-2286 (2003).

Yichao Wang, Toshimasa Uemura, Jian Dong, Hiroko Kojima, Junzo Tanaka, Tetsuya Tateishi, "Application of Perfusion Culture System Improves In vitro and In vivo Osteogenesis of Rat Bone Marrow-Derived Osteoblastic Cells In Porous Ceramic Materials," *Tissue Engineering,* **9(6)**, 1205-1214 (2003).

Hiroko Kojima, Toshimitsu Uede, Toshimasa Uemura, "In Vitro and In Vivo Effects of Overexpression of Osteopontin on Osteoblast Differentiation Using a Recombinant Adenoviral Vector," *J. Biochem* **136**, 377-386 (2004).

Hiroko Kojima, Toshimasa Uemura, "Strong and rapid Induction of osteoblast differentiation by Cbfa1/til-1 overexpression for bone regeneration," *Journal of Biological Chemistry* (2005) **280(4)**, 2944-2953.

4. I have read and am familiar with the above-identified patent application as well as the Official Action dated June 20, 2008, in the application.

5. I have read and am familiar with the contents of cited references, U.S. Patent Application Publication No. 2003/0235564 to Doll et al.; and U.S. Patent No. 5,030,611 to Ogawa et al. cited in the Official Actions in the above-identified application.

6. Based on my knowledge and experience in the art, and my review of the references, I provide the following comments.

Ogawa does not disclose adsorption of nucleic acids onto a bioadaptable material, but rather only discloses adsorption of acidic proteins onto a bioadaptable material. Furthermore, as recognized in Ogawa, the ability of a bioadaptable material to adsorb biomaterials such as acidic proteins depends on the method of manufacture of the bioadaptable material. For example, Ogawa identifies at column 1, lines 52-54 another method of producing hydroxyapatite, in which "disadvantageously the ability of the treated particles to adsorb acidic proteins such as bovine serum albumin (BSA) is lowered."

In addition to how the adsorption of acidic proteins onto bioadaptable porous materials depends on experimental conditions, the adsorption of nucleic acids onto a bioadaptable porous material such as a porous β-TCP also depends on conditions of incorporation. The adsorption efficacy of proteins or nucleic acids onto β-TCP is very low when β-TCP is merely mixed with a solution comprising proteins or nucleic acids. This is because porous β-TCP is a very light material and does not sink down into a solution when it is placed in the solution. Additionally, a solution can hardly penetrate into this material because the surface of the material is relatively

water repellant. Doll is silent as to how Runx2 is incorporated into the bioadaptable material.

However, a low pressure condition such as that used in the specification overcomes such problems and allows cells, proteins or viruses to penetrate into a porous β-TCP to directly contact the surface of the bioadaptable porous material. Thereby, adsorption can successfully occur.

The undersigned declares that all statements made herein of his own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the application or any patent issued thereon.

Hiroko Kojima

Hiroko KOJIMA

Signed this 9th. day of October, 2008.